

## **REMARKS**

### **Status of Claims**

Claims 1-4 and 6-47 are currently pending in the application. Claims 10-11, 15, 18-19, 23, 26-27, 31, 34-35, 39, 42-43, and 47 have previously been withdrawn from consideration, and remaining claims 1-4, 6-9, 12-14, 16-17, 20-22, 24-25, 28-30, 32-33, 36-38, 40-41, and 44-46 have been rejected by the Examiner in the Office Action of August 23, 2006.

Solely to expedite prosecution, in the present Response Applicants herein amend claims 1-4, 7, 44, and 46, and cancel claims 6, 8-9, 16-17, 24-25, 32-33, and 40-41. Applicants reserve the right to file a continuation or take other such action as is appropriate to preserve the subject matter removed by these amendments and cancellations. The amendments to the claims are supported by the specification as originally filed. No new matter has been added by way of these amendments.

After the amendments and cancellations of claims made in this Response, claims 1-4, 7, 10-15, 18-23, 26-31, 34-39, and 42-47 are pending, with claims 10-11, 15, 18-19, 23, 26-27, 31, 34-35, 39, and 42-43 withdrawn from consideration, and remaining claims 1-4, 7, 12-14, 20-22, 28-30, 36-38, and 44-46 rejected under 35 U.S.C. § 112, first paragraph, 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 103(a).

### **Priority**

Applicants respectfully submit herewith a certified copy of the NZ336259 application, as is required under 35. U.S.C. § 119(b). In light of this filing of the New Zealand priority document, Applicants respectfully request that the Examiner enter the claim to priority of this document.

**The Rejection Of The Claims Under 35 U.S.C. § 112, First Paragraph, As Lacking Adequate Enablement Has Been Obviated, And Must Be Withdrawn**

The Examiner has rejected all of the 31 non-withdrawn pending claims (i.e., claims 1-4, 6-9, 12-14, 16-17, 20-22, 24-25, 28-30, 32-33, 36-38, 40-41, and 44-46) under 35 U.S.C. § 112, first paragraph, as lacking adequate enablement. Specifically, the Examiner states that, although the specification enables claims for treating advanced or large tumor burdens with 1) the CAM "B7.1 in [sic] combined with DMXAA" and 2) "a cytokine comprising IL-2 plus analogues of XAA disclosed in the art" (see Office Action, page 3, upper half of page), the specification does not enable the use of "*any* CAM combined with *any* tumor restricted [sic] agent" (Office Action, last two lines of page 4; emphasis added).

With regard to this rejection, Applicants note at the outset that the standard for determination of adequate enablement is not whether *some* experimentation is required, but rather whether "any person skilled in the art can make and use the invention without *undue* experimentation" (Manual of Patent Examining Procedure (MPEP) § 2164.01, citing *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988); emphasis added). Thus the question with regard to the present rejection is whether the experimentation required to practice the invention as disclosed in the claims is actually undue, or whether it is in fact merely *routine*, with routine experimentation proof that the claims are enabled.

With regard to the claims, Applicants submit that the claims as they were previously presented to the Examiner required merely routine experimentation to practice, and that these claims as previously presented should therefore not have been rejected as nonenabled. In this regard, Applicants respectfully submit that the arguments provided by Applicants in the Response filed June 7, 2006, demonstrated that only *routine* experimentation would be required to practice those claims, and that on the basis of that earlier Response, the rejection of the claims should have been withdrawn.

Although the claims as previously presented should not have been rejected as nonenabled, solely in order to expedite prosecution Applicants have now altered the claims so that the recited CAM is not *any* CAM, but is, narrowly, one or more of 1) *only 5* explicitly recited CAMs ("a CAM selected from the group consisting of B7.1, B7.2, VCAM-1, MAdCAM-1, and ICAM-1," as recited in amended independent claims 1-4, and all of the remaining pending claims, which depend from these four independent claims); or, even more narrowly, 2) is only the *single* CAM B7.1 (claim 7).

Similarly solely to expedite prosecution, Applicants have now also altered the claims so that the recited tumor growth-restricting agent is only one or more of the *two* agents: 1) DMXAA, or 2) an agent which disrupts the expression or activity of hypoxia-inducible factor-1 (HIF-1) ("a tumor growth-restricting agent selected from the group consisting of DMXAA or an agent which disrupts the expression or activity of hypoxia-inducible factor-1 (HIF-1)"). With regard to these two agents, Applicants note that, in their previous species election, Applicants elected to pursue examination solely of an analogue of XAA, with rejoinder upon allowance of generic claims of the two other species FAA or an agent which disrupts the expression or activity of hypoxia-inducible factor-1 (HIF-1). Thus although claims 1-4 as currently amended refer to the non-elected species "an agent which disrupts the expression or activity of hypoxia-inducible factor-1 (HIF-1)," Applicants have included this non-elected species solely to make explicit reference to this species in the generic claims 1-4 which had previously *implicitly* contained this species in the broader language of those claims of "a tumor growth-restricting agent." Thus the explicit recitation of this non-elected species is no more than providing explicitly what had been previously implicit in the independent claims, and does not change the status of the claims with respect to the election of species or any action to later seek rejoinder of non-elected species.

In light of the alterations of the claims to recite 1) one or more of only 5 explicitly defined CAMs and 2) one or more of only 2 tumor growth-restricting agents, it is clear that the amount of experimentation required to enable the claims is merely *routine*, and that the rejections of the claims as nonenabled must be withdrawn. Specifically, there are 5 CAMs times 2 tumor growth-restricting agents, or only 10 pairwise combinations of CAMs and

tumor growth-restricting agents that the skilled artisan would have to use in order to practice the claims as currently presented. Given the state of the art for the practice of biological inventions such as that of the current invention, the practice of such 10 combinations is well within the routine practice of the skilled artisan. Therefore, it is clearly the case that the claims as currently presented are enabled.

Further in this regard, Applicants note that the claims as now presented render moot a concern of the Examiner's that analogues of XAA are problematic with regard to the amount of experimentation because "not all the analogue [sic] of XAA has [sic] a tumor restricted function" (Office Action, page 4, middle of second full paragraph). Specifically, the Examiner has noted that whereas two of the analogues of XAA in Futami et al. are useful for treating tumors under the specific conditions and protocols of this reference (i.e., 5-chloro-XAA and 5-methyl-XAA), Futami et al. are unable to obtain a similar effect using 7-chloro-XAA. While Applicants do not agree that this observation is any indication that the amount of experimentation required using analogues of XAA is anything other than routine, the Examiner's concerns in this regard are now rendered moot by the alterations of the claims that Applicants have provided solely to expedite prosecution.

In summary, in light of the arguments previously made by Applicants and further in light of the alteration of the claims to recite only 5 CAMs and only 2 tumor growth-restricting agents, it is clear that the amount of experimentation required to practice these claims is routine and not undue. Therefore, the rejection of these claims as not enabled has been obviated, and must be withdrawn.

**The Rejection Of The Claims Under 35 U.S.C. § 112, First Paragraph, As Lacking Adequate Written Description Has Been Obviated, And Must Be Withdrawn**

The Examiner has rejected all of the 31 non-withdrawn pending claims (i.e., claims 1-4, 6-9, 12-14, 16-17, 20-22, 24-25, 28-30, 32-33, 36-38, 40-41, and 44-46) under 35 U.S.C. § 112, second paragraph, as lacking adequate written description. Specifically, as the

Examiner correctly states, a showing of adequate written description requires a showing of "sufficient distinguishing identifying characteristics of the genus" (Office Action, page 5, 4<sup>th</sup> paragraph). In the instant case, the Examiner then goes on to state, the present invention provides a variety of specified CAMs and specified tumor growth-restricting agents.

"However," the Examiner then states,

"... the only combined therapy of a CAM and tumor growth restricting agent for treating a tumor disclosed in the specification is administering B7.1 in combination of [sic] DMXAA in mice to eradicate tumors (figure 2, 5, 8, 12, paragraph 98). The specification does not provide a method of using a CAM other than B7.1 in combination with any other tumor restricted agent [for] successfully treating or eradicating any large or advance tumors."

Therefore, the Examiner states later on the same page of the Office Action,

"Without experimentations [sic] for testing the specific CAM in combined [sic] with a specific tumor restricted agent in eradicating a large or advanced tumor successfully, one skilled in the art is not convinced the method would be successful for treating a large or advanced tumor and not convinced that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Thus, the Examiner concludes, the claims lack adequate written description.

With regard to the above argument made by the Examiner, Applicants respectfully state that it appears from the contents of this section of the Office Action that the Examiner is confusing the requirement of adequate written description with that of adequate *enablement*, since the above sections are directed to a discussion of the amount of *experimentation* required, and not to the actual requirement of written description of providing, as the Examiner initially stated, "sufficient distinguishing identifying characteristics of the genus" (see above).

With regard to this actual requirement for adequate written description of providing the identifying characteristics of the recited genus, as noted previously, solely in order to expedite prosecution, Applicants have now altered the claims to recite 1) one or more of only 5 explicitly defined CAMs and 2) one or more of only 2 tumor growth-restricting agents.

With regard to these compounds: 1) there can be no written description rejection regarding the explicitly defined CAMs, since the genus is limited and is explicitly defined; and, 2) there can similarly be no written description rejection for the limited and explicitly defined genus of 2 growth-restricting agents.

Therefore, since the claims as altered are drawn to a precisely limited and defined group of compounds, the rejection of the claims as lacking adequate written description has been obviated, and the rejection must be withdrawn.

**The Rejections Of The Claims Under 35 U.S.C. § 103(a) As Obvious Are Inapposite, And Must Be Withdrawn**

The Examiner has rejected all of the 31 non-withdrawn pending claims (i.e., claims 1-4, 6-9, 12-14, 16-17, 20-22, 24-25, 28-30, 32-33, 36-38, 40-41, and 44-46) under 35 U.S.C. § 103(a) as obvious over Futami et al. ("Futami") in view of Olsson ("Olsson"). Specifically, the Examiner asserts that 1) it would be obvious to combine these two references with 2) a reasonable expectation by the skilled artisan that such combination would be successful in providing results that 3) contain every limitation of every one of the rejected claims. Thus the Examiner concludes that, on these three bases, all 31 of the non-withdrawn pending claims are appropriately rejected.

With regard to this rejection, Applicants note that, as stated in MPEP § 2142, a showing of a *prima facie* case of obviousness by the Examiner requires that the Examiner demonstrate 1) motivation to combine the cited references with 2) a reasonable expectation of success, where such combination 3) teaches or suggests all the limitations of each of the rejected claims. As stated above, the Examiner has argued that the Examiner's rejection does satisfy each of these three requirements for a showing of *prima facie* obviousness. However, as Applicants will show below, in fact the Examiner's argument fails to satisfy *any* of these elements for a showing of *prima facie* obviousness, and therefore the Examiner's rejection of the claims as obvious must be withdrawn.

*1. Because the Examiner has failed to show the first element of a prima facie case for obviousness – i.e., motivation to combine the references – the Examiner's rejection of all of the claims must be withdrawn.*

First, the Examiner's rejection of all of the claims must be withdrawn because the Examiner has failed to demonstrate any motivation to combine Futami and Olsson, i.e., has failed to provide the first requirement of a showing of a *prima facie* case of obviousness.

Specifically, Futami discusses 1a) the treatment of *cancer* with a combination of FAA derivatives and 1b) the *single exogenously administered purified cytokine IL-2*, while Olsson 2a) does not teach or discuss any form of cancer whatsoever but instead teaches *T cell activation* 2b) *not* resulting in the single exogenously administered purified cytokine IL-2, but instead producing a *multiplicity of heterogeneous* effects including 2b1) T cell proliferation, 2b2) production of multiple cytokines (see Olsson, "Introduction") and 2b3) production of multiple other proteins, e.g., multiple transcription factors including AP-1, NF- $\kappa$ B, CD28RE, and NF-AT (see Olsson, page 504, bottom of left column).

In light of the above, there can be no motivation whatsoever to combine Futami with Olsson, and particularly no motivation for the rationale that the Examiner claims of substituting the single exogenously administered purified cytokine IL-2 of Futami with the situation in Olsson of endogenous IL-2 that would be obtained along with T cell activation, proliferation, and the slew of multiple cytokines and transcription factors produced by administration of a CAM. Futami teaches a treatment for cancer; Olsson never discusses cancer. Futami teaches purified exogenous IL-2; Olsson teaches CAM administration that produces a raft of effects and proteins. Futami does not teach or suggest the use of CAMs, and indeed never mentions CAMs; Olsson does not teach the use of CAMS in cancer at all, much less the use of CAMs in cancer to produce IL-2s otherwise exogenously administered in purified form, much less CAMs as replacements for IL-2 in combination with FAA derivatives. Although the Examiner states in the Office Action that "because Olsson et al. have suggested that IL-2 is induced by a CAM, B7.1, one of ordinary skill in the art would

have been motivated with a reasonable expectation of success to replace IL-2 with B7.1 in the method taught by Futami et al. for treating tumor” (Office Action, page 8, end of page), in light of the above, there is clearly no basis for the Examiner’s conclusion.

Thus on the basis of the above it is clear that the Examiner has failed to provide any evidence to support the first element of a *prima facie* showing of obviousness, i.e., a showing of motivation to combine the references. On this basis alone the Examiner’s rejection of the claims as obvious must be withdrawn.

*2. Because the Examiner has failed to show the second element of a prima facie case for obviousness – i.e., a reasonable expectation of success – the Examiner’s rejection of all of the claims must be withdrawn.*

The Examiner’s failure to provide any evidence to support the first element of a *prima facie* showing of obviousness (i.e., a showing of motivation to combine the references) is sufficient basis for the withdrawal of the rejection of the claims as obvious. However, a second reason why this rejection must be withdrawn may be found in the fact that the Examiner has failed to shown the second element of a *prima facie* showing of obviousness, i.e., has failed to show a reasonable expectation of success when these references are combined.

Specifically, even assuming some motivation to obtain the purified exogenously administered IL-2 of Futami by the administration of CAM to produce IL-2 that the Examiner states is clearly asserted in Olsson, the fact that CAM produces so many other effects and other factors would negate any reasonable expectation of success in the results of this replacement that one of ordinary skill might have. Thus as stated in MPEP § 2143.02, obviousness “does not require absolute predictability, however, *at least some degree of predictability* is required” (emphasis added). In the instant case, the use of a CAM that produces such enormous changes in cellular and protein conditions would not be expected by the skilled artisan to have any predictable effect relative to the administration of a single purified protein; therefore, there can be no reasonable expectation of success in the



combination of Futami and Olsson, even assuming that there is any motivation for such combination (which, as Applicants have shown above, there is not).

By way of further illustration of this lack of reasonable expectation of success, Applicants direct the Examiner's attention to the fact that Futami teaches the peritoneal application of 1 dose of 30,000 U of purified recombinant IL-2 on only each of days 8-11 post FAA administration. In contrast, substitution of this purified IL-2 with CAM would produce 1) *multiple effects* (T cell proliferation, multiple transcription factor and cytokine production) of 2) *unknown magnitude* (e.g., it is not clear how much IL-2 would accumulate as a result of any particular level of CAM) and 3) *uncertain duration* (it is not clear how long these effects based on T cell activation/proliferation would last, whereas purified injected IL-2 will have known half life and other pharmacokinetics). Given these multiple and uncertain effects, the skilled artisan would not expect any reasonable expectation of success in replacing the IL-2 of Futami with the CAM of Olsson, even if there were sufficient motivation to combine these references, which as Applicants have already shown, there is not.

Given the above discussion, there is no reasonable expectation of success required to satisfy the second element of a showing of a *prima facie* case of obviousness, and the rejection of the claims as obvious must be withdrawn.

*3. Because the Examiner has failed to show the third element of a prima facie case for obviousness – i.e., that the combination of references teaches every limitation of every rejected claim – the Examiner's rejection of all of the claims must be withdrawn.*

The Examiner's failures to provide any evidence to support the first or second elements of a *prima facie* showing of obviousness are, by themselves, sufficient bases for the withdrawal of the rejection of the claims as obvious. However, a third reason why this rejection must be withdrawn may be found in the fact that the Examiner has failed to show the third element of a *prima facie* showing of obviousness, i.e., has failed to show that the combination of Futami and Olsson, even when combined, teach *each and every limitation* of each of the rejected claims.

Specifically, the Examiner asserts that, despite the fact that the 31 rejected claims each have different limitations, *all* these claims are obvious based on what the Examiner asserts to be the teaching in the combination of Futami and Olsson of a subset of only three of the numerous limitations of these claims, i.e.: 1) the limitation of the use of "an analogue of XAA or DMXAA"; 2) the limitation of the additional use of a CAM comprising, e.g., B7.1; and, 3) the limitation that this combination of XAA/DMXAA analogue with a CAM is to be used for the treatment of "any advance [sic] or large tumor."

In fact, however, this combination of references -- and the three limitations the Examiner states that they provide -- do not provide the limitations of the rejected claims and therefore both *can not* and *do not* render obvious these claims.

In this regard, Applicants direct the Examiner's attention to the explicit limitation in all the claims that the methods of treatment of these claims must be successful for situations where there are "advanced or large" tumors or tumor burdens (see independent claims 1-4). As Applicants have stated previously, neither Futami nor Olsson teach or remotely suggest the treatment of cancers with "advanced or large" tumors or tumor burdens. Therefore, the combination of these references similarly cannot teach this limitation, and, in light of this absence of teaching of this limitation, the *prima facie* case for obviousness has not been provided and the rejection must be withdrawn.

In further support of the above, Applicants note that the experimental methods used by Futami additionally support the undeniable conclusion that this reference does not teach the treatment of "advanced or large" tumors or tumor burdens. Specifically, in Futami, tumor cells were injected intrarenally and the injected animals were then treated only 7 days after tumor injection. By contrast, in the present invention, the model system is focused specifically on extremely large tumors of 0.6 - 0.9 cm (i.e., tumors just short of a size requiring animal euthanasia) that, for this non-limiting model system, required localized and presumably nondiffusing administration of tumor cells into the left flank of the mouse followed by a long period of tumor growth of anywhere from about 14 to about 21 days. See

paragraph titled "Experimental Tumor Model," specification page 13. Given the short length of time for tumor growth in Futami as well as the likely diffusion of tumor cells in this reference relative to in the non-limiting model system of the present invention, it is clear that the experimental methods of Futami also support the conclusion given above that Futami does not teach or suggest the limitation of all of the claims of the present invention of "advanced or large" tumors or tumor burdens, i.e., that this reference alone or in combination with Olsson does not provide every limitation of the claims, and therefore that the obviousness rejection must be withdrawn.

In addition to the lack of a teaching in Futami or Olsson of the explicit limitation of all the claims of treatment for "advanced or large" tumors or tumor burdens, these references also do not teach other limitations of subsets of the claims, and therefore on this basis additionally fail to satisfy the third element of a showing of a *prima facie* case of obviousness. For example, neither reference teaches or suggests the use of DMXAA or HIF-1, both of which are explicit limitations of all of the claims.

Similarly, in claims 12, 20, 28, 36, and 44, the tumor growth-restricting agent is administered *after* the administration of the CAM, and in claims 13, 21, 29, 37, and 45, the time of administration of growth-restricting agent is explicitly specified as being *12 to 48 hours after* administration of the CAM. By contrast, Futami teaches the administration of tumor growth-restricting agent fully 168 hours (7 days) *before* administration of IL-2, i.e., 168 hours *before* administration of what the Examiner claims is the desired product of the administration of CAM (i.e., what is taught by Olsson). Although the Examiner states that, with regard to the timing of administration of compounds, "administering one reagent prior to another" would be *prima facie* obvious (see Office Action, page 8, end of second paragraph), based on the above it is impossible to see on what basis the Examiner is able to arrive at this conclusion.

In light of the above, Applicants respectfully submit that the Examiner clearly has not satisfied the third requirement for a showing of a *prima facie* case of obviousness, i.e., that the combination of references teaches every limitation of the claims. It is of course possible

that the Examiner believes that these additional limitations are "well known" in the art, and that they are therefore provided on this basis. If this is indeed the Examiner's belief, Applicants respectfully request that, as provided in MPEP § 2144.03C, "the examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding."

Finally with regard to the limitations provided in the claims, Applicants respectfully note that the Examiner has failed to understand the limitation of synergistic action of compounds that is explicitly provided in all the claims. Specifically, in responding to Applicants statements in the previous Response, the Examiner states "Applicants do not claimed [sic] a method of combination therapy [that] has the synergistic effect." Office Action, page 8, middle of last paragraph. In fact however, in direct contradiction to the Examiner's statement, *each and every one of the claims explicitly recites a limitation of a synergistic effect*. Specifically, with regard to the four independent claims from which all the other claims depend: claim 1 states that either agent alone "would be ineffective in eradicating an advanced or large tumor burden"; claim 2 states that the agents "are together effective to eradicate any advanced or large tumors"; claim 3 that the tumor growth-restricting agent "is effective, in combination with the immunotherapeutic [or CAM] agent to eradicate any advanced or large tumors"; and, claim 4 states that the CAM "acts in combination with said tumor growth restricting agent to eradicate an advanced or large tumors." By contrast, and as stated above, the combination of Futami and Olsson does not teach the synergistic combination of compounds for treatment of large tumors, nor does it teach the synergistic effect of any compound with DMXAA, which it does not teach at all.

Given the above arguments, it is clear that the Examiner has not shown that Futami and Olsson together teach or suggest every limitation of every claim, as is required to satisfy the third element of a showing of a *prima facie* case of obviousness. Therefore, on this basis the rejection of the claims as obvious must be withdrawn.

*Summary With Regard To Obviousness*

In light of the above discussion, it is clear that the Examiner has not provided any of the three elements required for a showing of *prima facie* obviousness. Specifically, the Examiner has not demonstrated 1) motivation to combine the cited references with 2) a reasonable expectation of success, where such combination 3) teaches or suggests all the limitations of each of the rejected claims. Therefore the Examiner's rejection of the claims as obvious must be withdrawn.

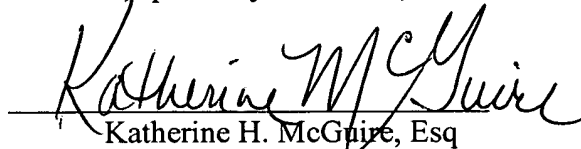
**CONCLUSION**

After the amendments and cancellations of claims made in this Response, claims 1-4, 7, 10-15, 18-23, 26-31, 34-39, and 42-47 are pending, with claims 10-11, 15, 18-19, 23, 26-27, 31, 34-35, 39, and 42-43 withdrawn from consideration, and remaining claims 1-4, 7, 12-14, 20-22, 28-30, 36-38, and 44-46 rejected under 35 U.S.C. § 112, first paragraph, 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 103(a). In light of the preceding discussions, Applicants submit that the rejections of the claims must be withdrawn and that the claims be allowed.

The Commissioner is hereby authorized to charge \$90.00 for the increase of the multiple dependant claim fee and any other fee that may have been overlooked to Deposit Account No. 10-0223.

Respectfully submitted,

Dated: 11/22/06

  
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